13 Prognosis of lung disease in cystic fibrosis children based on genotype modelling and lung function longitudinal data

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Although chronic lung disease is the most serious clinical expression of CF, and the majority of patients die from respiratory failure, a relationship between *CFTR* genotype and severity of pulmonary disease in CF has proven difficult to establish. Therefore, we investigated the relationship between CFTR genotype models based on molecular genetic criteria ((*i*) class I–V, (*ii*) nature of mutations, (*iii*) gene regions, (*iv*) protein regions, (*v*) nature and localisation of mutations, (*vi*) specific genotypes) and the progression of lung disease based on lung function parameters (FRC_{pleth}, LCI, V_{TG}, sR_{eff}, FEV_1, FEF_{50}) in a well characterised cohort of 204 CF patients followed during a life span from 6 to 20 years. Linear mixed model (LMM) analyses were used to analyse the relationship between each lung function parameter and age in the genetic groups *i–vi*, the slope representing progression. We found that, depending on the nature and/or localisation of the mutations, discrimination between genetic subgroups resulted from different functional lung characteristics. Moreover, if genotypes are stratified according to the presence or absence of F508del and subgrouped according to the nature of mutations, discrimination can be achieved by all lung function parameters demonstrating best association with FRC_{pleth} and FEF_{50}. The data demonstrate that extended lung function evaluation is needed to provide evidence for genotype-phenotype associations in CF, and that genotype modelling may be a helpful prognostic tool even though it is beyond doubt that many other modifying factors contribute to the CF phenotype.

14 Association of clinical severity of cystic fibrosis (CF) with polymorphism D/I in *ACE* gene

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The *ACE* gene encodes angiotensin-converting enzyme is an enzyme related to pro-inflammatory response. This gene presents a polymorphism called D/I, the D allele is characterized by the deletion of 287pb in intron 16 and responsible for higher expression of the gene.

Objective: To link the polymorphism D/I in *ACE* gene with the clinical markers of CF (Shwachman score, body mass index-BMI, age at diagnosis, early pulmonary and gastrointestinal symptoms, microorganisms present, spirometry, oxygen saturation).

Method: 181CF patients, 95 (52.6%) males, mean age 15 years. For the analysis of polymorphism D/I was used the technique of PCR. Statistical analysis was performed by SPSS v.10.0. The analysis of quantitative data was performed by analysis of variance for a factor and qualitative data by logistic regression test and Odds Ratio (OR).

Results and Discussion: For patients with allele D, the diagnosis was made on average before the three years of age when compared to individuals homozygous II (OR: 3.07, CI = 1.1–2.6). As for the appearance of the table digestive same occurred (OR: 8.2, CI = 1.4–1.5). As for the Shwachman score, was observed a greater number of patients with genotype DD with scores classified as severe (OR: 6.4, CI = 1.2–34.2). These results suggest that increased expression of ACE resulting of DD genotype leads to greater lung damage due to inflammation. But the genotype DD seems to protect against chronic infection that can be observed by the presence of greater numbers of patients with genotype II infected by the bacteria *Achromobacter xylosoxidans* (OR: 4.5, CI = 1.2–17.1; RR: 3.5, CI = 1.3–9.7).

Conclusion: The polymorphism D/I in the *ACE* gene acts as modifier in CF.

15 Polymorphisms in *GCLC* and *GST*(*M1*, *T1* and *P1*) genes and their performance in clinical severity of cystic fibrosis (CF)

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For the present study were chosen candidate genes related to modifying the mechanism of action of glutathione (GSH).

Objective: To link the presence of polymorphisms (pol.) of *GST* and *GCLC* genes with the degree of seriousness.

Method: 181 patients, 52.6% males, mean age: 15 years. We used the technique of PCR in the genes *GSTM1* and *T1* for the *GSTP1* (pol.313A/G) and *GCLC* (pol.129C/T and 350A/G) genes was also used restriction enzyme. The data were correlated with: Kanga (EK) and Shwachman (ES) score, BMI, age at diagnosis, onset of symptoms, isolated microorganisms, spirometry and SaO2. Statistical analysis was performed by analysis of variance for a factor, logistic regression test and Odds Ratio (OR).

Results: For the *GSTM1*, *GCLC* (pol.129C/T) and *GSTP1* gene weren't statistically significant correlation with clinical markers. For the *GSTT1* gene, individuals with at least one allele coding, were classified in the category of low BMI (OR:3.1, CI=1.4–7.1), when *GSTM1* and *T1* genes were analyzed simultaneously, the same occurred (OR:1.5, CI=1.1–2.7). Patients with *M1* and *T1* genes with null alleles had the lowest SaO2 (OR:4.3, CI=1.2–20.1) and worst ranking for ES (OR:9.0, CI=1.5–55.1). Regarding the association of bacterial colonization to null allele for *T1* and coding to *M1* was related to the presence of *Pseudomonas aeruginosa mucoid* (OR:3.1, CI=1.3–7.6) *and non mucoid* (OR:4.8, CI=1.7–13.7). For GCLC350(A/G) pol. of the *GCLC* gene was found a association to genotype A/A with SaO2 (OR:5.8, CI=2.3–14.5) and with worse rating for EK, lower value of FEF25–75% and FEV1/FVC, and more severe regarding FEV1 (OR:4.6, CI=1.3–5.2).

Conclusion: *GSTM1*, *GSTT1* and *GCLC* (pol.350A/G) genes act as modifiers in CF.

16 Nasal polyposis and cystic fibrosis: review of literature and case report

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Objective/hypothesis: The aim of this study was to address whether nasal polyposis (NP) might be a factor associated with a lower severity of cystic fibrosis (CF).

Study design: We collected data of literature on NP as a unique or associated sign in CF and reviewed the clinical and molecular aspects of CF associated with NP.

Methods:

1. We carried out a comprehensive analysis of literature on CF patients with and without NP, using the Pubmed site. We reviewed CF genotypes and clinical severity in NP(+) vs. NP(–) patients, lung function, *P. aeruginosa* infection, nutritional and pancreatic status.
2. Furthermore, we analyzed the CFTR gene in a 26 years old patient with isolated severe NP as the single feature of CF.

Results:

1. This literature study showed a "milder" phenotype in "NP+" vs. "NP–" CF patients, contrasting with a marked association between NP and "severe" CF mutations.
2. In addition, we identified a complex genotype, four heterozygous variants, namely p.Q493X (a severe mutation) on the paternal allele, p.V562I, p.A1006E, (TG)11(T)5 (IVS8–5T) on the maternal allele, in a CF case presenting as isolated NP.

Conclusions: We speculate that genetic/environmental factors associated with NP might attenuate the functional impact of "severe" CF mutations. Furthermore, over representation of CF carriers among patients with isolated NP, advocates CFTR molecular screening in such a population for genetic counselling purpose.

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